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IMPROVEMENT OF THERAPY FOR PATIENTS WITH LOCALIZED SCLERODERMA

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Localized scleroderma is a chronic multifactorial autoimmune disease affecting the skin and subcutaneous tissue. The aim of this study was to compare the clinical efficacy of two complex treatment regimens in patients with localized scleroderma combined with Lyme borreliosis. The study compared two regimens: one based on benzylpenicillin and the other on doxycycline hydrochloride 100 mg twice daily in 45 patients aged 20 to 64 years. Clinical manifestations, lesion activity using the modified Localized Scleroderma Skin Severity Index, and serum levels of pro-inflammatory interleukin-6 and anti-inflammatory interleukin-10 were evaluated before and 30 days after treatment. The results demonstrated a significantly greater reduction in skin lesion activity and pro-inflammatory interleukin-6 levels, alongside an increase in anti-inflammatory interleukin-10 in the doxycycline-treated group compared to benzylpenicillin. These results suggest that doxycycline hydrochloride offers superior clinical and immunological benefits in patients with localized scleroderma associated with Lyme borreliosis.

Key words: localized scleroderma, Lyme-borreliosis, cytokines, benzylpenicillin, doxycycline hydrochloride.

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УДОСКОНАЛЕННЯ ЛІКУВАННЯ ПАЦІЄНТІВ ІЗ ВОГНИЩЕВОЮ СКЛЕРОДЕРМІЄЮ

Вогнищева склеродермія – це хронічне мультифакторне аутоімунне захворювання, що уражає шкіру та підшкірну тканину. Метою дослідження було порівняти клінічну ефективність двох комплексних схем лікування у пацієнтів із вогнищевою склеродермією, поєднаною з бореліозом Лайма. Було порівняно дві схеми лікування: на основі бензилпеніциліну та доксицикліну гідрохлориду 100 мг двічі на добу у 45 пацієнтів віком від 20 до 64 років. Оцінювали клінічні прояви, активність уражень за модифікованим індексом вогнищевої склеродермії, а також рівень прозапального інтерлейкіну-6 та протизапального інтерлейкіну-10 у сироватці крові до та через 30 днів після лікування. Результати показали значно більше зниження активності уражень шкіри та рівня інтерлейкіну-6, а також збільшення інтерлейкіну-10 у групі, що отримувала доксициклін, порівняно з бензилпеніциліном. Отримані дані свідчать про перевагу доксицикліну гідрохлориду у клінічному та імунологічному покращенні стану пацієнтів із вогнищевою склеродермією, асоційованою з бореліозом Лайма.

Ключові слова: вогнищева склеродермія, хвороба Лайма, цитокіни, бензилпеніцилін, гідрохлорид доксицикліну.

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Localized scleroderma (morphea) is a chronic multifactorial autoimmune disease primarily affecting the skin and subcutaneous tissues, characterized by a prolonged progressive course with sequential phases of inflammation, fibrosis, and atrophy [1, 3, 5]. The clinical manifestations vary widely, ranging from limited plaques to extensive skin involvement, often leading to cosmetic deformities and functional impairments that reduce patients' quality of life [2, 4]. Despite advances in understanding its pathogenesis, timely diagnosis and effective treatment remain challenging due to the heterogeneous presentation and the complex underlying mechanisms [7, 9].

Recent studies have highlighted the significant role of infectious agents, particularly tick-borne pathogens such as Borrelia burgdorferi sensu lato, in the etiopathogenesis of localized scleroderma [2, 4]. The immunopathology involves both cellular and humoral immune responses that disrupt the balance between pro-inflammatory and anti-inflammatory cytokines, with interleukin-6 (IL-6) and interleukin-10 (IL-10) being key biomarkers reflecting disease activity and therapeutic response [4, 10]. Understanding these immune dynamics is essential for developing targeted treatment strategies that combine antimicrobial and immunomodulatory approaches.

Currently, clinical guidelines for managing localized scleroderma complicated by Lyme disease are limited, and there is insufficient evidence comparing the effectiveness of different antibiotic regimens [5, 10]. In particular, the comparative efficacy of benzylpenicillin and doxycycline in this patient population warrants further investigation to optimize therapeutic outcomes.

The purpose of the study was to compare the clinical efficacy of two complex treatment regimens in a patient with localized scleroderma and Lyme disease using benzylpenicillin sodium or doxycycline hydrochloride.

Materials and methods. The study was conducted at the "National Pirogov Memorial Medical University", the "Vinnytsia Regional Clinical Skin and Venereological Center", and the "Ministry of Health of Jordan". A total of 45 patients aged 20 to 64 years with localized scleroderma (LS) combined with Lyme borreliosis (LB) were observed from 2019 to 2024, including 11 men (24.4 %) and 34 women (75.6 %). Patients received both inpatient and outpatient care. The diagnosis of LS and LB was based on clinical signs in accordance with ICD-10 criteria. Lyme borreliosis was confirmed serologically using ELISA (Euroimmun AG, Germany) for IgM and IgG antibodies to Borrelia burgdorferi sensu lato, following the manufacturer's guidelines. A control group of 25 healthy blood donors, matched by age and sex, was also evaluated.

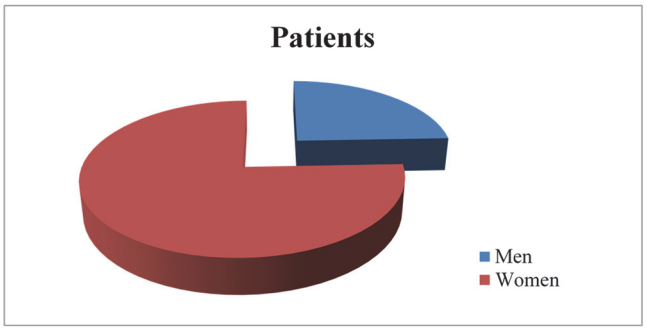

Fig. 1. Categories of patients by gender.

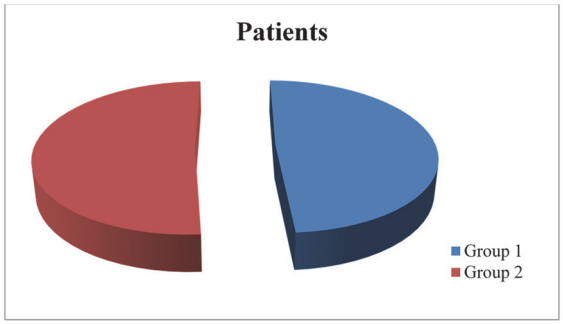

Fig. 2. Categories of patients by group.

Levels of pro-inflammatory interleukin-6 (IL-6) and anti-inflammatory interleukin-10 (IL-10) were measured in the patients' blood sera using ELISA, both before the beginning of therapy and 30 days after its completion. The reference values were set at up to 10 pg/ml for IL-6 and up to 31 pg/ml for IL-10. Two different complex treatment regimens were used depending on the group assignment.

All patients were randomly divided into two study groups. The first group included 22 patients who received treatment for 21 days. The regimen included intramuscular injections of benzylpenicillin sodium (Biochemik LLC, Russia) at a dose of 1 million units six times a day. Additionally, patients were administered Plaquenil (Sanofi, France) at 0.2 grams orally in three five-day cycles separated by three-day breaks. Karsil (KRKA, Slovenia) was given as two tablets three times a day, Aevit (Kyiv Vitamin Plant JSC, Ukraine) as a single daily dose of 100,000 units, Thiotriazolin 2.5 % solution (Arterium Corporation, Ukraine) as a 4.0 ml intramuscular injection, and Solcoseryl gel (Meda AB, Sweden) was applied topically to affected skin areas.

In the second group, which consisted of 23 patients, the treatment was identical except that benzylpenicillin sodium was replaced by oral administration of doxycycline hydrochloride (Pfizer, USA) at a dose of 100 mg twice daily.

The effectiveness of each treatment regimen was assessed 30 days after therapy. Evaluation included clinical symptoms, local skin changes, and cytokine dynamics in blood serum. Lesion activity was assessed using a modified Localized Scleroderma Skin Severity Index (mLoSSI), considering emergence of new lesions or enlargement of existing ones, erythema intensity at lesion margins, and density of affected areas compared to surrounding healthy skin. These indicators were assessed over 18 anatomical regions, including head, neck, torso, limbs, and extremities.

Statistical analysis was conducted using the STATISTICA software package. Non-parametric methods were applied, specifically the Wilcoxon signed-rank test for paired comparisons and the Mann-Whitney U test for group comparisons. This study is part of the comprehensive scientific research work of the Department of Infectious Diseases with Epidemiology, Skin and Venereal Diseases.

Results of the study and their discussion. The study involved a total of 45 patients who had been diagnosed with localized scleroderma (LS) in combination with Lyme borreliosis (LB). The patients ranged in age from 20 to 64 years and included 11 men (24.4 %) and 34 women (75.6 %), reflecting the known higher prevalence of LS among females. All patients received treatment and were followed up between 2019 and 2024 across several medical institutions that participated in the observation. The diagnoses of localized scleroderma were established on the basis of clinical signs and consistent with criteria set forth by the ICD-10 classification system. Lyme borreliosis was confirmed through serological testing using the enzyme-linked immunosorbent assay (ELISA), which identified the presence of specific antibodies to Borrelia burgdorferi.

To ensure comparability of immune and inflammatory parameters, a control group comprising 25 healthy individuals was also examined. The controls were matched with the patient group by both age and sex, which minimized confounding variables related to these demographic factors. All individuals in the control group were confirmed to have no history of autoimmune disease or tick-borne infections and displayed normal clinical and laboratory profiles.

The 45 patients with confirmed LS and LB were divided into two treatment groups. Each group received a 21-day course of therapy, differing in the type of antibacterial agent administered. Group 1 consisted of 22 patients who were treated with benzylpenicillin sodium via intramuscular injection. This was administered six times per day in accordance with standard dosing intervals for severe infections. In addition to the antibiotic, patients in this group received several adjunctive therapies: hydroxychloroquine sulfate (Plaquenil) to address autoimmune mechanisms, hepatoprotector Karsil to support liver function during polypharmacy, the multivitamin Aevit to enhance antioxidant protection, the metabolic agent Thiotriazolin to support cellular metabolism, and topical Solcoseryl gel to promote local tissue regeneration in affected skin areas.

Group 2 included 23 patients and followed the same adjunctive regimen as group 1; however, the antibiotic used was oral doxycycline hydrochloride, administered twice daily. Doxycycline was selected due to its known anti-inflammatory and anti-fibrotic properties in addition to its antimicrobial activity against Borrelia species. The choice to compare intramuscular benzylpenicillin with oral doxycycline reflects clinical practice considerations, as both are employed in the management of LB-related conditions, although their systemic effects may differ.

At baseline, prior to initiation of therapy, all patients demonstrated elevated serum levels of the proinflammatory cytokine interleukin-6 (IL-6), although values remained within the upper limit of the reference range (up to 10 pg/ml). Nonetheless, when compared to the control group, the elevation in IL-6 among patients was statistically significant. Conversely, levels of the anti-inflammatory cytokine interleukin-10 (IL-10) were reduced in patients relative to healthy controls, indicating a systemic proinflammatory milieu and impaired regulation of immune responses.

Clinically, the most frequent complaints reported by patients before treatment included sensations of tightness, tingling, and itching in the areas of scleroderma lesions. These symptoms were distributed similarly in both treatment groups. In addition to cutaneous manifestations, many patients experienced systemic symptoms, including fever, persistent headaches, arthralgia (joint pain), joint swelling, and generalized fatigue. These symptoms are consistent with active inflammatory and infectious processes and are often observed in patients with systemic involvement or co-infection with Borrelia.

After 30 days of therapy, both groups showed clinical improvement, but the extent differed significantly. The modified Localized Scleroderma Skin Severity Index (mLoSSI) decreased slightly in group 1 (benzylpenicillin) to 9.29 ± 0.98 points. In contrast, group 2 (doxycycline) demonstrated a more pronounced and clinically meaningful reduction from 9.11 ± 0.93 to 3.27 ± 0.21 points, indicating a significant regression in disease activity and improved skin condition. Although this difference did not always reach statistical significance ($p > 0.05$), the trend clearly favored doxycycline therapy in reducing lesion severity and inflammation.

In group 1, symptoms such as itching decreased marginally, while reports of tightness and tingling sensations significantly dropped from 31.8 % to 13.6 %. Both groups initially experienced general symptoms, including fever, headache, joint pain, and fatigue. However, by day 30, only group 1 showed a statistically significant reduction in fever cases, declining from 13.6 % to 4.5 %, suggesting some differential systemic effects between the treatment regimens.

Table 1

Dynamics of complaints related to scleroderma foci in patients with LS associated with LB under different treatment regimens (M±m)

Complaints	Group 1, n=22				Group 2, n=23			
	before treatment		after treatment		before treatment		after treatment	
	abs	%	abs	%	abs	%	abs	%
Tightness and/or tingling sensation	7	31.8	3	13.6	8	34.7	2	8.7
Itching	8	36.3	5	22.7	9	39.1	3	13.0
Fever	3	13.6	1	4.5	2	8.7	0	0
Headache	3	13.6	2	9.1	3	13.6	0	0
Joint pain	6	27.3	4	18.2	8	34.8	3	13.6
Swelling of the joints	4	18.2	3	13.6	5	21.7	1	4.3
Fatigue/general weakness	7	31.8	5	22.7	9	39.2	2	8.7

Changes in immune parameters paralleled the clinical improvements observed. Serum IL-6 levels decreased significantly in both groups after treatment, indicating reduced inflammatory activity. However, the reduction was more pronounced in group 2 (doxycycline), where IL-6 dropped from 9.04 to 4.01 pg/ml, approaching levels seen in the healthy control group. This suggests a more effective suppression of proinflammatory signaling, likely due to doxycycline's combined antimicrobial and immunomodulatory effects.

In contrast to IL-6, the anti-inflammatory cytokine IL-10 showed a significant increase, especially in group 2, rising from 15.78 to 32.45 pg/ml. This cytokine shift reflects a favorable immune response, demonstrating improved regulation of inflammation and enhanced anti-inflammatory activity in patients treated with doxycycline hydrochloride compared to benzylpenicillin.

Table 2

Dynamics of IL-6 and IL-10 (pg/ml) in the serum of patients with LS associated with LB under different treatment regimens

Indicator	Control group, n=25	Group 1, n=22		Group 2, n=23	
IL-6 (0–10)	0.43	before treatment	after treatment	before treatment	after treatment
		9.41	8.32	9.04	4.01
IL-10 (0–31)	0.15	16.52	18.16	15.78	32.45

Alongside IL-6 reductions, serum IL-10 concentrations increased markedly in both groups, suggesting restoration of anti-inflammatory balance. The most substantial increase was again noted in group 2, where IL-10 rose from 15.78 to 32.45 pg/ml, exceeding even the levels observed in healthy controls. This suggests not only suppression of inflammation but active promotion of immune regulation and tissue recovery. The higher IL-10 levels in the doxycycline group may indicate a broader immunomodulatory impact, contributing to better clinical outcomes and potentially less fibrotic progression.

The combination of clinical and laboratory findings strongly supports the conclusion that both treatment regimens – benzylpenicillin and doxycycline-based – are effective in reducing disease activity in patients with localized scleroderma associated with Lyme borreliosis. However, doxycycline demonstrates a broader therapeutic potential due to its multifaceted pharmacological effects, including antimicrobial and immunomodulatory actions. These properties may provide additional benefits in managing complex autoimmune skin conditions with infectious triggers, such as localized scleroderma in the context of Lyme disease [1, 5, 6].

The superior performance of doxycycline may be attributed to its multifaceted pharmacological properties. In addition to its antibacterial activity against Borrelia, doxycycline is known to inhibit matrix metalloproteinases, suppress production of proinflammatory cytokines, and reduce fibrotic signaling pathways. These characteristics make it particularly suitable for conditions such as LS, where inflammation and fibrosis are central features [1, 5, 8].

Furthermore, while both treatment groups experienced reductions in systemic symptoms such as joint pain and fatigue, only the group receiving benzylpenicillin showed a statistically significant reduction in fever frequency. This isolated finding may reflect differential responses to bacterial endotoxins or individual variability in immune reactivity, and warrants further investigation [3, 5].

In conclusion, doxycycline hydrochloride appears to be a more effective treatment option than benzylpenicillin for patients with localized scleroderma associated with Lyme borreliosis. Its dual antimicrobial and immunomodulatory actions result in improved clinical outcomes, enhanced cytokine balance, and potential slowing of fibrotic progression. Persistent elevations in IL-6 in some individuals despite therapy may indicate ongoing subclinical inflammation and highlight the need for long-term monitoring. Future research should explore extended treatment durations, combination therapies, and the potential of cytokine profiling to guide individualized therapy in LS patients with coinfections. [4, 6, 10].

Conclusions

1. The use of doxycycline hydrochloride instead of benzyl penicillin in the combined treatment of patients with localized scleroderma associated with Lyme disease contributes to a faster resolution of general and local manifestations of inflammation in morphological epithelioma lesions, which is achieved by improving Local skin reduction was demonstrated to be approximately 2.9-fold and 1.5-fold in severity.

2. Compared with benzyl penicillin, doxycycline hydrochloride led to faster resolution of fever and headache in study patients, and a significantly lower percentage of patients with fatigue/massiness, joint pain and swelling.

3. The tested regimen of complex treatment with doxycycline hydrochloride significantly reduced the concentration of the pro-inflammatory cytokine IL-6 in the patient's blood compared to penicillin – 2.3-fold vs. 1.1-fold reduction and the anti-inflammatory component IL-10 – 2.1 and 1.1 times respectively.

4. Doxycycline hydrochloride should be used instead of benzyl penicillin in the comprehensive treatment of patients with localized scleroderma associated with Lyme disease.

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